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2024 Update of Chinese Guidelines for Diagnosis and Treatment of Hyperuricemia and Gout Part I: Recommendations for General Patients

Mingshu Sun¹ | Zhaohui Lyu² | Can Wang³ | Yan Li⁴ | Dongbao Zhao⁵ | Xingwu Ran⁶ | Haibing Chen⁷ | Benli Su⁸ | Xiangyun Chang⁹ | Ping Liu¹⁰ | Dewen Yan¹¹ | Xiuyun Jiang¹² | Kang Chen² | Jiaqing Shao¹³ | Xiaochun Teng¹⁴ | Yongli Yao¹⁵ | Yuming Li¹⁶ | Ying Chen³ | Jidong Cheng¹⁷ | Zhifeng Cheng¹⁸ | Zhen Liu³ | Fengjing Liu¹⁹ | Xinyu Li²⁰ | Huiyong Yin²¹ | Chao Liu²² | Hsiao-Yi Lin²³ | Yaolong Chen²⁴ | Wen-Chan Tsai²⁵ | Ronald M. L. Yip²⁶ | Changgui Li¹⁷ | Jiajun Zhao¹²

¹Department of Rheumatology, Xiang'an Hospital of Xiamen University, Xiamen, China | ²Department of Endocrinology, the First Medical Center of Chinese PLA General Hospital, Beijing, China | ³Department of Metabolism, the Affiliated Hospital of Qingdao University, Qingdao, China | ⁴Department of Endocrinology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China | ⁵Department of Rheumatology, the First Affiliated Hospital of Naval Medical University (Shanghai Changhai Hospital), Shanghai, China | ⁶Department of Endocrinology, West China Hospital, Sichuan University, Chengdu, China | ⁷Department of Endocrinology and Metabolism, Shanghai Tenth People's Hospital, Tongji University School of Medicine, Shanghai, China | ⁸Department of Endocrinology and Metabolism, Second Hospital of Dalian Medical University, Dalian, China | ⁹Department of Endocrinology, the First Affiliated Hospital of Shihezi University, Xinjiang, China | ¹⁰Department of Endocrinology, School of Medicine, the Second Affiliated Hospital, The Chinese University of Hong Kong, Shenzhen & Longgang District People's Hospital of Shenzhen, Shenzhen, China | ¹¹Department of Endocrinology, Shenzhen Second People's Hospital, the First Affiliated Hospital of Shenzhen University, Shenzhen, China | ¹²Department of Endocrinology, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, China | ¹³Department of Endocrinology, Affiliated Jinling Hospital, Medical School of Nanjing University, Nanjing, China | ¹⁴Department of Endocrinology and Metabolism, the First Hospital of China Medical University, Shenyang, China | ¹⁵Department of Endocrinology, Qinghai Provincial People's Hospital, Xining, China | ¹⁶Department of Endocrinology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology (HUST), Wuhan, China | ¹⁷Department of Endocrinology, Xiang'an Hospital of Xiamen University, Xiamen, China | ¹⁸Department of Endocrinology, the Fourth Affiliated Hospital of Harbin Medical University, Harbin, China | ¹⁹Department of Endocrinology, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China | ²⁰Department of Endocrinology, Central Hospital of Dalian University of Technology (Dalian Municipal Central Hospital), Dalian, China | ²¹Department of Biomedical Sciences, City University of Hong Kong, Hong Kong, China | ²²Department of Endocrinology, Affiliated Hospital of Integrated Traditional Chinese and Western Medicine, Nanjing University of Chinese Medicine, Nanjing, China | ²³Division of Allergy Immunology and Rheumatology, Cheng-Hsin General Hospital, National Yang Ming Chiao Tung University, Taipei, Taiwan | ²⁴Research Unit of Evidence-Based Evaluation and Guidelines, Chinese Academy of Medical Sciences (2021RU017), School of Basic Medical Sciences, Lanzhou University, Lanzhou, China | ²⁵Department of Rheumatology, Chung-Ho Memorial Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan | ²⁶Tung Wah Group of Hospitals Integrated Diagnostic and Medical Centre, Kwong Wah Hospital, Kowloon, China

Correspondence: Changgui Li (changguili@vip.163.com) | Jiajun Zhao (jjzhao@sdu.edu.cn)

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ABSTRACT

Background: In 2018, the Chinese Society of Endocrinology developed the “Chinese guideline for diagnosis and treatment of hyperuricemia and gout (2019)”. Over the past 5 years, clinical and experimental research has expanded our knowledge of gout,

Mingshu Sun and Zhaohui Lyu contributed equally to this work.

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resulting in novel diagnostic and therapeutic approaches. This update, prompted by new clinical challenges and gaps in evidence, aims to refine the 2019 guidelines.

Methods: The working group formulated clinical questions based on a nationwide questionnaire survey, and the expert panel evaluated new evidence addressing these questions from January 2019 to March 2025. The guideline development followed the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach, adhering to internationally recognized protocols for clinical practice guideline development.

Results: The update includes 26 recommendations addressing 10 clinical questions related to urate-lowering therapy (ULT) for asymptomatic hyperuricemia and reproductive populations, anti-inflammatory treatments, urine alkalinization, dietary advice, and gout diagnosis in patients without a record of hyperuricemia and gout flare predictions in patients with asymptomatic hyperuricemia and intermittent gout. It recommends febuxostat as a first-line ULT for asymptomatic hyperuricemia and using it with caution during pregnancy and lactation. ULT should be customized according to the pathophysiologic type of hyperuricemia. Chronic gout management includes maintaining serum urate levels between 180 and 300 $\mu\text{mol/L}$ and prolonged glucocorticoid tapering in combination with colchicine. Alkalinization with citrate is preferred over sodium bicarbonate for patients with urine pH < 6.0. Novel biomarkers for predicting gout flares are proposed for high-risk populations.

Conclusions: These updated guidelines incorporate expert consensus and evidence to provide refined strategies for the diagnosis, prevention, and treatment of hyperuricemia and gout.

1 | Introduction

Gout is a prevalent inflammatory metabolic dysfunctional disease induced by the deposition of monosodium urate (MSU) crystals in joints and soft tissues. Hyperuricemia, defined by elevated concentration of serum urate (SU) exceeding the saturation threshold of 420 $\mu\text{mol/L}$ (7 mg/dL), is a primary risk factor for the development of gout. The treatment paradigm includes long-term urate-lowering therapy (ULT) to reduce SU levels, dissolve MSU crystals, and prevent and manage recurrent flares. However, recent data indicate an increase in both the prevalence and burden of gout globally.

Gout management involves several disciplines in China, like rheumatology, endocrinology, nephrology, and general internal medicine. By following national standardized procedures and protocols for the development of clinical evidence-based guidelines [1, 2], the Chinese Society of Endocrinology, Chinese Medical Association launched in 2018 and accomplished with multidisciplinary experts the Chinese Guidelines for Diagnosis and Treatment of Hyperuricemia and Gout (2019) (2019 Guideline). The 2019 Guideline developed a series of recommendations, especially on stratified gout diagnosis and ULT for asymptomatic hyperuricemia and gout, and considerations for pathophysiologic type-guided ULT and urine alkalization [3]. The guideline was widely adopted. However, evidence supporting several recommendations was not so strong, and several clinical problems prompted then were not included due to insufficient evidence.

During the past 5 years, emerging studies revealed new developments in gout management. Recent national/regional guidelines, including the 2021 Asia-Pacific League of Associations for Rheumatology (APLAR) [4] and the 2023 Hong Kong Society of Rheumatology (HKSR) [5] guidelines, have provided some of the advances. Others, such as evidence concerning adjunctive therapies and prediction biomarkers of gout flares, do not arouse sufficient attention [6, 7]. The evolving body of research necessitated an update of the 2019 guidelines. The Chinese Society of Endocrinology initiated this 2024 Update of Chinese Guidelines for Diagnosis and Treatment of Hyperuricemia and Gout (2024

Update), aiming to provide refined evidence-based recommendations, considering emerging therapies, diagnostic tools, and clinical insights.

2 | Methods

The 2024 Update was developed following the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology, incorporating evidence from systematic literature reviews (SLRs), standardized evidence quality assessment, and expert consensus, supported by the Lanzhou University GRADE Center. Based on the evidence quality classification (A, B, C, and D) (Table S1), and considering other factors such as cost, accessibility, and the balance of benefits and harms, we form the strength of recommendations. The grade of recommendations is determined as grade 1, recommend to or not to use, and grade 2, suggested to or not to use (Table S2).

A guidance steering committee of five senior specialists was established to oversee the processing of the guideline. A multidisciplinary expert panel (EP) was assembled with experts in clinical practice and research of gout from all over China, for clinical question proposals, approval for the suggestions and statements composition, including 20 endocrinologists, 12 rheumatologists, 7 experts in nephrology, gastroenterology, and cardiology, and 2 methodologists. A working group of 11 junior endocrinologists was also organized to implement the process of guideline development.

Clinical questions were proposed through a review of guidelines and expert consensus published since 2019, and a national questionnaire survey. The EP discussed at the first face-to-face meeting, incorporating clinical evidence and physicians' input, finalized 10 key questions for the 2024 Update, which were deconstructed using the Patient/Population, Intervention, Comparison, Outcome (PICO) principle (Table S3). A second questionnaire among the EP ranked outcome indicators by importance (Table S4).

Evidence retrieval was developed among China Biomedical Literature Database, CNKI, Wanfang, VIP, PubMed, Web of

TABLE 1 | Ten clinical questions and the literature distribution of each evidence body.

Questions	Distribution of evidence (chapter)			
	Systematic review/ meta analysis	Original research	Guidelines/consensus	Others
Urate-lowering therapy in asymptomatic hyperuricemia	4 Meta analyses 2 Systematic reviews	3 RCTs 2 Cohort studies	1 Guideline 3 Consensuses	0
Urate-lowering therapy guided by renal urate excretion	0	2 RCTs 1 Cohort studies	2 Guidelines 1 Consensus	0
Anti-inflammatory therapy with glucocorticoids for recurrent gout	2 Meta analyses 3 Systematic reviews	4 RCTs	3 Guidelines 2 Consensuses	1 Book
Management for chronic gouty arthritis	1 Systematic review	0	3 Guidelines 1 Consensus	0
Urine alkalization	1 Meta analysis 1 Systematic review	3 RCTs 1 Cross-sectional study 1 Crossover-controlled study 1 Cohort study	0	0
Dietary management	2 Meta analyses 2 Systematic reviews	3 RCTs 3 Cross-sectional studies 2 Case-Control studies 2 Cohort studies	0	0
Gout management in women of reproductive period	0	1 Cross-sectional study 4 Case reports	2 Guidelines 2 Consensuses	0
Gout management in men of reproductive period	1 Meta analyses	2 Cohort studies 1 Case report	2 Guidelines	0
Diagnosis of normouricemic gout	1 Meta analysis 1 Systematic review	1 RCT 1 Cohort study	3 Guidelines	0
Assessment of gout flare risk	1 Systematic review	5 Cohort studies 5 Case-Control studies	0	0

Abbreviation: RCT, randomized controlled trial.

Science, Cochrane Library, Embase, and guideline databases for studies published between January 2019 and January 2024. Prior to the publication of the guidelines (March 1, 2025), the evidence panel performed a rapid evidence review across all relevant questions to prevent oversight of the most recent evidence.

A total of 40 guidelines/consensus and 505 articles were retrieved. After removing duplicates and articles not within the scope of the clinical questions, 17 systematic reviews, 50 original studies, and 24 previous guidelines/consensus were included, forming the evidence base for the recommendations.

The preliminary results of the SLRs were presented to EP members during the second face-to-face meeting. The recommendations were drafted and revised in two meetings and two rounds of Delphi voting. A 10-point Likert scale was used to rate agreement, with consensus achieved when over 80% of the EP members rated a recommendation ≥ 7 . In very few cases, a good practice statement (GPS) may be used, representing the opinions of the EP members. One patient representative was invited to comment on the recommendations. The final version of the

recommendations will be distributed through publications, academic meetings, and so forth.

The overall procedure is summarized in the flow chart (Figure S1). This guideline was registered (IPGRP, <http://www.guidelines-registry.org>) (PREPARE-2024CN563).

3 | Results

The PICO questions and the corresponding evidences were presented to the EP (Table 1). Finally, 25 recommendations reached consensus (Table 2, Figure 1).

3.1 | Urate-Lowering Therapy in Asymptomatic Hyperuricemia

For patients with asymptomatic hyperuricemia, first-line ULT options include febuxostat, allopurinol, and benzbromarone; long-term ULT is generally recommended, with discontinuation considered for patients maintaining $SU \leq 360 \mu\text{mol/L}$ for three

TABLE 2 | Recommendations with grades (GoR), levels of evidence (LoE), and levels of agreement (LoA).

Recommendations	PICO question	GoR	LoE	LoA (%)
Urate-lowering therapy in asymptomatic hyperuricemia				
1. For patients with asymptomatic hyperuricemia, first-line ULT options include febuxostat, allopurinol and benzbromarone	1	1	A	95.2
2. Long-term ULT is generally recommended, with discontinuation considered for patients maintaining SU $\leq 360 \mu\text{mol/L}$ for three months or $< 240 \mu\text{mol/L}$ on two separate occasions. The decision should involve lifestyle modification and regular SU monitoring	2	GPS		88.7
Urate-lowering therapy guided by renal urate excretion				
3. The classification of hyperuricemia, based on 24-h renal urate excretion (UUE) and fractional excretion of renal urate (FEUA), is recommended to guide ULT selection	3	2	C	91.9
4. For renal underexcretion, benzbromarone is the preferred agent	3	2	C	93.5
5. For combined hyperuricemia (UUE between 600 and 700mg), low dose febuxostat and an add-on low dose benzbromarone if necessary are suggested	3	2	C	96.8
Anti-inflammatory therapy with glucocorticoids for recurrent gout				
6. For recurrent gout, glucocorticoids are suggested to be tapered down slowly, generally within one month	10	2	D	98.4
7. Colchicine is recommended to prevent flares during glucocorticoid tapering	10	2	B	96.8
8. IL-1 inhibitors are suggested for patients unresponsive to conventional therapies	10	2	B	100
Management for chronic gouty arthritis				
9. For chronic gouty arthritis, ULT should aim to maintain SU levels between 180 and $300 \mu\text{mol/L}$	11	1	C	98.4
10. Flare prophylaxis is suggested to continue for at least 3 months after achieving target SU levels if there is no evidence of tophi	11	2	C	100
11. If tophi present, prophylaxis is suggested to continue for at least 6 months after achieving target SU levels and the dissolution of tophi	11	2	C	100
Auxiliary therapy: Urine alkalization				
12. Urine alkalization is suggested for patients with hyperuricemia and gout, particularly those with a morning urine pH < 6.0 and taking uricosuric agents	4	2	C	98.4
13. Citrate preparations are preferred; Sodium bicarbonate is an alternative for patients who cannot tolerate citrate or have renal impairment	4	2	C	98.4
14. The dosage of alkalization agents should be adjusted to maintain morning urine pH levels between 6.2 and 6.9	4	2	C	98.4
Auxiliary therapy: Dietary management				
15. Dietary restrictions on high-purine foods, high-fructose products, and alcohol are recommended	5	2	B	98.4
16. While dietary fiber, tart cherry products, citric acid products, and skim milk are encouraged	5	2	C	100
Gout management in women of reproductive period				
17. Lifestyle interventions should be prioritized. Benzbromarone and allopurinol are contraindicated during pregnancy, while febuxostat can be used cautiously. Allopurinol can be used during lactation	6	2	D	98.4

(Continues)

TABLE 2 | (Continued)

Recommendations	PICO question	GoR	LoE	LoA (%)
18. Low-dose glucocorticoids, colchicine, and nonsteroidal anti-inflammatory drugs (NSAIDs) are acceptable for managing gout flares	8	2	D	98.4
Gout management in men of reproductive period				
19. For men planning conception, discontinuation of allopurinol and febuxostat is recommended for at least 3 months in those with suspected infertility during treatment. Benzbromarone is recommended if necessary	7	2	D	93.5
20. Low-dose glucocorticoids, colchicine, and NSAIDs are suggested for managing gout during this period	9	2	D	93.5
Diagnosis normouricemic gout				
21. The presence of MSU crystals in synovial fluid is recommended as the gold standard for diagnosing gout in patients with normouricemia	12	1	C	100
22. For those who cannot undergo joint aspiration or have negative results, alternative diagnostic tools such as ultrasound, dual-energy CT (DECT), and X-ray are recommended to detect MSU crystal deposits	12	2	B	100
23. Repeated SU assessment two weeks after a joint episode is recommended to obtain the authentic SU level to follow the 2015 ACR/EULAR diagnostic criteria	12	2	B	100
Assessment of gout flare risk				
24. Imaging techniques such as ultrasound and DECT, are suggested to be used to assess flare risk in patients with gout or asymptomatic hyperuricemia	13	2	B	98.4
25. Biomarkers like baseline SU, are suggested to be used to assess flare risk in patients with gout or asymptomatic hyperuricemia	13	2	C	96.8

Abbreviations: ACR, American College of Rheumatology; DECT, dual-energy CT; EULAR, European Alliance of Associations for Rheumatology; FEUA, fractional excretion of uric acid; GPS, good practice statement; IL-1, interleukin-1; MSU, monosodium urate; NSAIDs, nonsteroidal anti-inflammatory drugs; PICO, population, intervention, comparison, outcome; SU, serum urate; ULT, urate-lowering therapy; UUE, urinary urate excretion.

months or $<240\mu\text{mol/L}$ on two separate occasions. The decision should involve lifestyle modification and regular SU monitoring.

Patients with asymptomatic hyperuricemia and $\text{SU} \geq 9\text{mg/dL}$, or those with comorbidities such as cardiovascular, metabolic dysfunction, and kidney diseases, should initiate ULT as per the 2019 Guideline [3]. Febuxostat is either comparable to or more effective than allopurinol in terms of urate-lowering efficacy [8, 9], and is safer in patients with severe chronic kidney disease (CKD) [10]. In patients with CKD stage 3a and asymptomatic hyperuricemia, febuxostat provides better renal protection than benzbromarone [10]. Although febuxostat has received a boxed warning from the U.S. Food and Drug Administration for increased risk of mortality in patients with cardiovascular comorbidities following the CARES trial, a recent global meta-analysis did not show significant differences in cardiovascular outcomes between febuxostat (40 or 80mg per day) and allopurinol (200–300mg per day) [8]. Furthermore, Asians have a higher risk of allergic reaction to allopurinol due to the prevalence of HLA-B*5801, which may affect the risk–benefit ratio in the Chinese population.

Allopurinol is recommended by guidelines in many countries as a first-line treatment in patients with asymptomatic hyperuricemia. Compared to allopurinol, benzbromarone may reduce the risk of dialysis by approximately 50% in patients with asymptomatic hyperuricemia and CKD. Benzbromarone has urate-lowering effects similar to those of febuxostat [11], and is

particularly effective in patients with poor renal urate excretion [11]. Therefore, both allopurinol and benzbromarone are recommended as first-line treatment.

Currently, there is insufficient evidence to support discontinuing medication in patients with asymptomatic hyperuricemia. A small subset of patients may be able to maintain SU levels below $360\mu\text{mol/L}$ through diet, exercise, and management of metabolic syndrome. Meta-analyses suggest that excessively low SU levels are associated with an increased risk of neurodegenerative diseases. Therefore, we suggest that patients on low-dose urate-lowering agents who maintain SU levels $\leq 360\mu\text{mol/L}$ for 3 months or achieve SU levels below $240\mu\text{mol/L}$ on at least two separate occasions may consider discontinuing ULT, provided they maintain a healthy lifestyle and regularly monitor their SU levels.

3.2 | Urate-Lowering Therapy Guided by Renal Urate Excretion

The classification of hyperuricemia, based on 24-h urinary urate excretion (UUE) and fractional excretion of renal urate (FE_{UA}), is recommended to guide ULT selection; for renal underexcretion, benzbromarone is the preferred agent, while for combined hyperuricemia (UUE between 600 and 700 mg), low-dose febuxostat and an add-on low-dose benzbromarone if necessary are suggested.

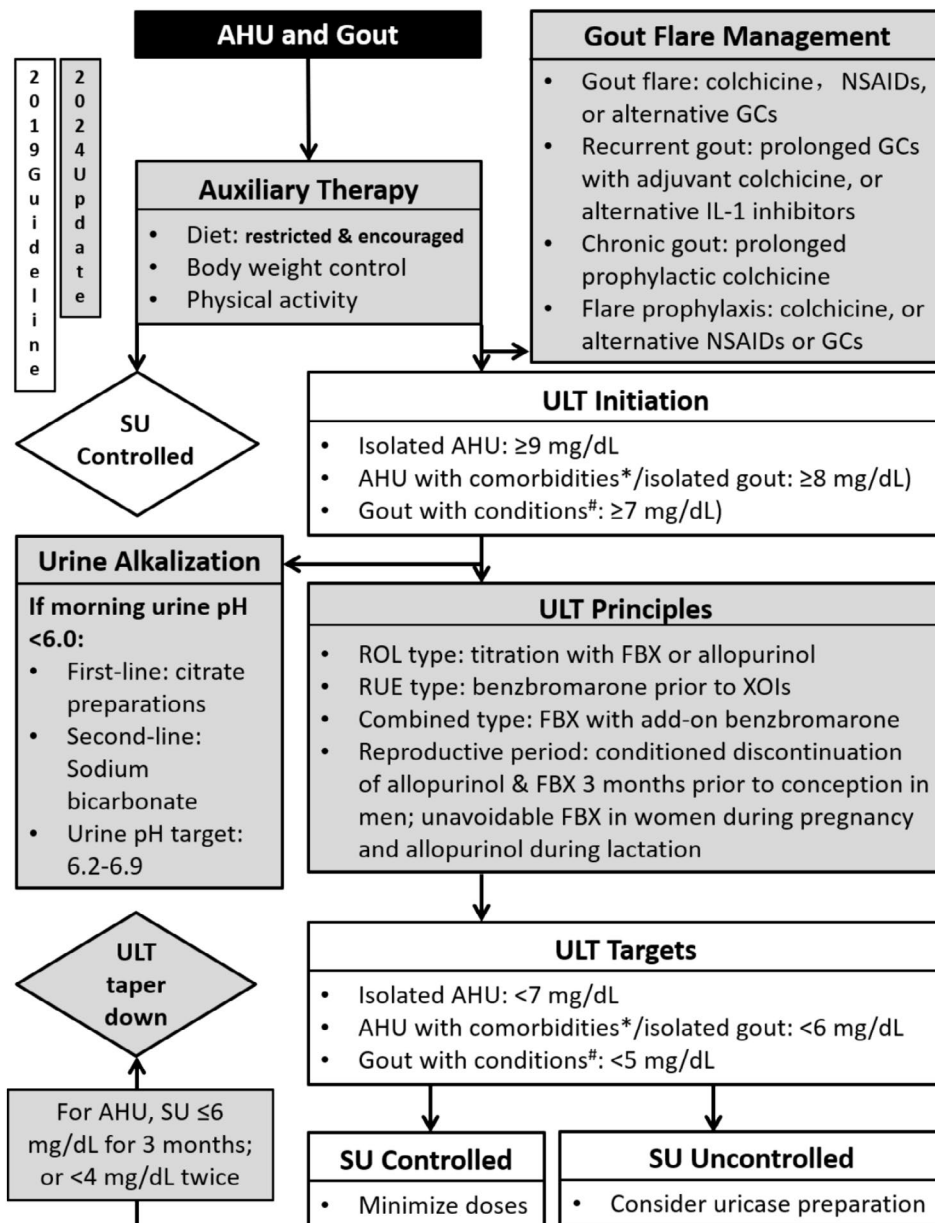


FIGURE 1 | Summary of the recommendations on management of patients with asymptomatic hyperuricemia and gout. 2019 Guideline, Guideline for the Diagnosis and Treatment of Hyperuricemia and Gout in China (2019). *Chinese Journal of Endocrinology and Metabolism*. 2020;36(1):13. <https://rs.yiigle.com/cmaid/1179377>; *, comorbidities including hypertension, dyslipidemia, diabetes, obesity, stroke, coronary heart disease, heart failure, uric acid nephrolithiasis, chronic kidney disease (CKD $\geq$ stage 2); #, conditions including gout flare ≥ 2 times/year, tophi, chronic gouty arthritis, nephrolithiasis, chronic kidney disease, hypertension, diabetes, dyslipidemia, stroke, ischemic heart disease, heart failure, and gout onset age < 40 years old; AHU, asymptomatic hyperuricemia; FBX, febuxostat; GCs, glucocorticoids; IL, interleukin; NSAIDs, non-steroidal anti-inflammatory drugs; ROL, renal overload; RUE, renal underexcretion; SU, serum urate; ULT, urate-lowering therapy; XOIs, xanthin oxidase inhibitors.

The 2019 Guideline clarified that hyperuricemia classification should be determined based on a combination of baseline UUE and FE_{UA} [3]. The 2016 European Alliance of Associations for Rheumatology (EULAR) guideline recommended assessing renal urate excretion prior to initiating ULT in gout patients with early onset or a family history of early onset to guide medication selection [12].

A randomized controlled trial (RCT) conducted in Chinese gout patients with renal urate underexcretion found that benzbromarone (25 mg/day) was more effective than febuxostat (20 mg/day) in achieving SU target levels, with fewer

occurrences of abnormal liver function [11]. A cohort study conducted over 3 months showed that benzbromarone (25 mg/day) led to a higher SU target achievement rate in patients with renal underexcretion compared to unclassified patients [13]. However, it should be avoided in patients with UUE > 700 mg on a low-purine diet or > 800 mg on a regular diet, which indicate a dominant renal urate overload due to the possibility of renal damage [14]. A RCT study demonstrated that adding benzbromarone (25 mg/day) to febuxostat (20 mg/day) achieved superior urate-lowering efficacy compared to febuxostat monotherapy in gout with combined hyperuricemia over three months [15].

3.3 | Anti-Inflammatory Therapy With Glucocorticoids for Recurrent Gout

Glucocorticoids initiated for recurrent gout flare are suggested to be tapered down slowly, generally within 1 month; Colchicine is recommended to prevent flares during glucocorticoid tapering; IL-1 inhibitors are suggested for patients unresponsive to conventional therapies.

Systemic or intra-articular glucocorticoids have been proved and suggested by previous guidelines for short-term use in gout flares [5, 16–18]. For patients with recurrent gout (≥ 2 episodes per year), particularly those experiencing flares within 3 months after the last episode, or those not receiving prophylactic treatment during ULT, the tapering period may be extended to 14 or even 21 days, accompanying a low dose of colchicine. However, the total course of glucocorticoids therapy should adhere to the “Guidelines for Clinical Application of Glucocorticoid Drugs (2023 Edition)”, which generally limits short-term use to 1 month.

The 2020 American College of Rheumatology (ACR) guidelines for gout management conditionally recommend IL-1 inhibitors for patients who are unresponsive or intolerant to conventional anti-inflammatory therapy [2]. Anakinra was shown to be not superior to a single dose of triamcinolone (40 mg injection) when administered at 100 or 200 mg/day for 5 days. Rilonacept showed comparable efficacy to indomethacin when administered as a 320 mg subcutaneous injection. Canakinumab significantly alleviated pain and inflammation and reduced the risk of flares in patients with acute gouty arthritis with a single 150 mg dose. Recently, an express letter reported that firsekibart, a fully humanized IL-1 β inhibitor administered as a single 200 mg subcutaneous injection, compared with compound betamethasone, demonstrated non-inferior pain relief for acute gout attack and superior efficacy in delaying new flares within 6 months among Chinese patients [19]. Current evidence suggests that IL-1 inhibitors are effective and safe for patients with gout flares who are unsuitable for standard therapies [20].

3.4 | Management for Chronic Gouty Arthritis

For chronic gouty arthritis, ULT should aim to maintain SU levels between 180 and 300 $\mu\text{mol/L}$; flare prophylaxis is suggested to continue for at least 3 months after achieving target SU levels if there is no evidence of tophi; if tophi are present, prophylaxis is suggested to continue for at least 6 months after achieving target SU levels and the dissolution of tophi.

The primary goal in managing chronic gout is to maintain SU at lower levels to promote the dissolution of crystals and, in some cases, tophi. The 2012 ACR guidelines for gout management recommend maintaining SU level $< 6 \text{ mg/dL}$ for all gout patients, and $< 5 \text{ mg/dL}$ for those with tophi [21]. These targets were reaffirmed by the 2023 consensus recommendations of the Hong Kong Society of Rheumatology [5].

Guidelines also recommend low-dose colchicine, NSAIDs, or low-dose corticosteroids for gout flare prophylaxis for at least 3 months (for those without tophi) or at least 6 months (for those

with tophi), with the duration potentially extended based on the dissolution status of tophi [22, 23]. In chronic gout, maintaining a constant, safe level of SU is crucial to prevent recurrent crystal formation and inflammation. Therefore, the EP reached consensus that prophylaxis treatment should not be discontinued until the SU target is stable for 3–6 months, depending on the presence of tophi.

IL-1 inhibitors are a newer class of drugs for the treatment of acute gout. Some studies have explored the use of IL-1 inhibitors as prophylactic agents, showing promising results; however, infection must be ruled out before administration, particularly in chronic gouty arthritis.

3.5 | Auxiliary Therapy: Urine Alkalization

Urine alkalization is suggested for patients with hyperuricemia and gout, particularly those with a morning urine pH < 6.0 and taking uricosuric agents; citrate preparations are preferred; sodium bicarbonate is an alternative for patients who cannot tolerate citrate or have renal impairment; the dosage of alkalization agents should be adjusted to maintain morning urine pH levels between 6.2 and 6.9.

Excessively acidic urine is a key factor in the formation of uric acid stones. Urine alkalization can dissolve existing stones and prevent the formation of new ones [24]. A cross-sectional study found that those with a urine pH ≤ 5.0 were at higher risk of renal damage [25]. A study has shown that allopurinol combined with citrate preparations significantly increased urine pH and FE_{UA} , while effectively reducing SU levels. Therefore, urine alkalization is recommended for hyperuricemia and gout patients, especially those on uricosuric agents, when the morning urine pH is < 6.0 .

Citrate preparations have been found to be of comparable efficacy on urine alkalization but more effective in reducing gout flares, hematuria, urine albumin-to-creatinine ratio (UACR), and kidney stones and in improving the serum lipid profile [6, 26, 27]. Prolonged sodium bicarbonate use may increase sodium load, which heightens the risk of hypertension and promotes urinary calcium excretion, potentially increasing the likelihood of calcium stone formation. In summary, citrate preparations are considered the preferred agents for urine alkalization in patients with gout and asymptomatic hyperuricemia, while sodium bicarbonate should be used in cases of intolerance to citrate preparations or when renal impairment and metabolic acidosis are present.

The dosage of urine alkalization medications is primarily determined by urine pH levels. The goal is to maintain a morning urine pH between 6.2 and 6.9, which helps reduce the risk of uric acid kidney stones and promotes their dissolution. The recommended treatment duration is currently 3–6 months [6].

3.6 | Auxiliary Therapy: Dietary Management

Dietary restrictions on high-purine foods, high-fructose products, and alcohol are recommended; while dietary fiber, tart cherry products, citric acid products, and skim milk are encouraged.

Excessive intake of purine-rich food or ingredients that interfere with purine metabolism (such as fructose) or urate excretion (such as alcohol) may lead to hyperuricemia, and a low-purine diet benefits the gout population in reducing sUA levels and cardiovascular-metabolic conditions, particularly in those with the urate overproduction phenotype [28]. Certain dietary patterns, such as the Mediterranean diet and DASH diet (the dietary pattern in Dietary Approaches to Stop Hypertension), are beneficial for patients with gout by improving hyperuricemia and metabolic syndrome. These diets are more beneficial compared to the western diet, which is characterized by high purine, fat, and calorie content [29, 30].

The consumption of carbohydrates, particularly fructose-containing soft drinks, can exacerbate metabolic diseases and further elevate SU levels. Alcohol metabolism produces lactic acid, which reduces renal clearance of uric acid and decreases its excretion [31]. Certain alcoholic beverages, such as beer, contain high levels of purines, which can directly elevate SU levels. Additionally, alcohol increases the release of purines within the body, which are subsequently metabolized into uric acid, leading to elevated SU levels.

Dietary fiber helps support blood sugar control, improves insulin resistance, and promotes uric acid excretion [32]. Tart cherry preparations and citric acid products can alkalize urine, effectively reduce the frequency of gout flares, and lower SU levels [6, 33]. Population studies have also indicated that, compared to other protein sources, milk does not elevate SU levels [34].

3.7 | Gout Management in Women of Reproductive Period

Lifestyle interventions should be prioritized. Benzbromarone and allopurinol are contraindicated during pregnancy, while febuxostat can be used cautiously. Allopurinol can be used during lactation. Low-dose glucocorticoids, colchicine, and non-steroidal anti-inflammatory drugs (NSAIDs) are acceptable for managing gout flares.

Hyperuricemia during pregnancy is associated with adverse outcomes. Due to the lack of established diagnostic criteria for hyperuricemia during pregnancy and lactation, unclear initiation of treatment and targets, and insufficient clinical evidence for urate-lowering medication for pregnant or lactating women, SU levels should primarily be managed through appropriate dietary and lifestyle modifications to ensure the safety of the fetus and nursing infants.

A systemic review suggests that allopurinol use during pregnancy may have teratogenic effects, especially during the first trimester [35]. Most guidelines recommend against the use of benzbromarone and allopurinol in pregnant women. Febuxostat may be considered only when the benefits outweigh the potential risks to the fetus. A case report showed that oxypurinol, the active metabolite of allopurinol, was detectable with low concentration in breast milk of a lactating woman taking 300 mg/day of allopurinol, and relatively low levels in the infant's plasma 2 h after breastfeeding, without adverse events after 6 weeks'

exposure [36]. The American Academy of Pediatrics considers allopurinol compatible with breastfeeding.

During gout flares, low-dose glucocorticoids, colchicine, and NSAIDs are generally considered safe and effective.

Overall, medication use during pregnancy and lactation should be carefully evaluated, weighing the risks and benefits, with consideration for the potential effects on both mother and infant.

3.8 | Gout Management in Men of Reproductive Period

For men planning conception, discontinuation of allopurinol and febuxostat is recommended for at least 3 months in those with suspected infertility during treatment. Benzbromarone is recommended if necessary. Low-dose glucocorticoids, colchicine, and NSAIDs are suggested for managing gout during this period.

Recent studies have indicated that hyperuricemia negatively affects sex hormones, semen quality, and contributes to erectile dysfunction (ED), while the impact of urate-lowering drugs on male fertility and pregnancy outcomes remains unclear. One study reported temporary infertility in a patient treated with allopurinol, with sperm penetration test scores returning to normal after discontinuation [35]. A cohort study found that febuxostat may pose a higher risk of ED compared to allopurinol in male gout patients [37]. A prospective cohort study concerning the effects of allopurinol, febuxostat, and benzbromarone on sperm quality and sex hormones found that benzbromarone increased sperm concentration, while febuxostat exposure decreased sperm motility at three months [38]. However, the decision of ULT discontinuance should be based on a balanced risk/benefit evaluation. The 2016 EULAR recommendations on antirheumatic drugs during pregnancy and lactation, as well as the 2020 ACR guidelines on reproductive health management for patients with rheumatic and musculoskeletal diseases, suggest that men can use low-dose NSAIDs, colchicine, and tumor necrosis factor inhibitors during the conception period [39].

3.9 | Diagnosis of Moneuricemic Gout

The presence of MSU crystals in synovial fluid is recommended as the gold standard for diagnosing gout in patients with normouricemia. For those who cannot undergo joint aspiration or have negative results, alternative diagnostic tools such as ultrasound, dual-energy CT (DECT), and X-ray are recommended to detect MSU crystal deposits. Repeated SU assessment 2 weeks after a joint episode is recommended to obtain the authentic SU level to follow the 2015 ACR/EULAR diagnostic criteria.

Although elevated SU is a primary driver for MSU crystal formation and serves as an independent risk factor for gout flares, not all patients experience high SU levels during flare episodes. During gout flares, SU levels tend to decrease temporarily [40]. Therefore, for patients highly suspected of having gout, if their SU levels are normal during joint episodes, or do not meet the

diagnostic criterion, it is recommended to recheck the SU level at least 2 weeks after the episode resolve [41].

In any cases, the presence of MSU crystals in synovial fluid or tophi remains the gold standard for diagnosis, as recommended in both the 1977 American Rheumatism Association criteria and the 2015 ACR/EULAR classification criteria [42]. For patients who cannot undergo joint aspiration or present negative results, newly developed technologies like DECT and ultrasonography are alternative diagnostic tools for patients without a history of hyperuricemia [43].

3.10 | Assessment of Gout Flare Risk

Imaging techniques such as ultrasound and DECT, along with biomarkers like baseline SU, are suggested to be used to assess flare risk in patients with gout or asymptomatic hyperuricemia.

Gout flares not only cause severe pain, but they have also been recently linked to significant cardiovascular and cerebrovascular complications. Predicting and preventing flares in patients with intercritical gout or asymptomatic hyperuricemia is important for both healthcare providers and patients. Studies have demonstrated that the presence of MSU crystal deposition, confirmed via ultrasound and/or DECT, is a risk factor for flares within 1–2 years [44, 45]. These imaging modalities can also forecast the frequency of flares in joints with MSU crystal deposition following the initiation of ULT [46]. A systematic review revealed a positive correlation between the volume of urate crystal deposits detected by DECT and the risk of future flares [45].

In recent years, biomarkers have been increasingly used to support both the diagnosis and prediction of gout flares. Emerging biomarkers and multi-omics predictive models have shown potential in forecasting gout flares and frequent attacks [7, 47, 48]. A prospective cohort study involving 193 gout patients identified serum cancer antigen (CA) 72-4 as an independent risk factor for gout flares [47]. A cohort study investigating patients with infrequent or frequent gout, using mass spectrometry-based untargeted metabolomics, established a predictive model for frequent gout attacks [7]. Another cohort study also identified seven characteristic metabolic markers that distinguish gout from hyperuricemia using mass spectrometry [48]. However, these findings require further validation through multicenter and prospective studies.

4 | Discussion

This 2024 Update strengthens and expands many of the recommendations presented in the 2019 Guideline, integrating novel evidences, multidisciplinary expert consensus, and patient perspectives. These recommendations focus on ULT for asymptomatic hyperuricemia and individuals in the reproductive phase, ULT guided by renal urate excretion criteria, special anti-inflammatory treatment strategies, diagnosis for normouricemic gout, prediction of gout flares, urine alkalization, and dietary modifications regarding SU levels and inflammation. By offering clear guidance on these previously ambiguous issues, the update provides optimized management options for gout and hyperuricemia patients, addressing issues not adequately

covered in national/regional clinical practice guidelines from APLAR, HKSR, and the Taiwan consensus [4, 5, 14].

The treating serum urate-to-target strategy has consistently been acknowledged as the principle of managing gout and asymptomatic hyperuricemia at risk [1–3, 14]. The 2019 Guidelines have recommended stratified ULT targets based on disease burden factors such as tophi, flare frequency, comorbidities, and age at onset [3]. The question of whether ULT should be discontinued in long-term patients who have achieved target SU levels has been a significant clinical concern. Given the absence of long-term safety data for these ULT agents [10], the 2024 Update suggests discontinuing drugs under certain conditions and focusing on lifestyle management, which is similar to another guideline regarding lifestyle behaviours [49].

The determination of the first-line urate-lowering agent remains another contentious issue. The selection of an appropriate drug depends on several factors, including the individual patient's urate-lowering response, potential adverse effects, co-existing medicines, and pharmacoeconomic considerations. In light of recent high-quality clinical trial data [8, 9, 13, 15], the 2024 Update recommends benzbromarone over XOIs in Chinese patients with renal urate underexcretion. For patients with combined hyperuricemia, a combination of low-dose febuxostat and benzbromarone is now preferred, rather than titrating febuxostat alone [14]. This renal urate excretion profile-guided ULT is underpinned by a cohort study in which subtypes of renal urate handling have subtype-specific clinical and genetic features [50].

Reproductive safety related to ULT has not been adequately addressed in prior guidelines. This updated guideline systematically reviewed the use of urate-lowering medications in specific populations, including pregnant women, lactating women, and men preparing for conception. Given the importance of these clinical issues and the acceptable strength of the available evidence, recommendations on gout management during the reproductive period of men and women were presented in the 2024 Update. However, balancing between benefit and damage and lifestyle modification is fully emphasized.

Gout has been identified as a heterogeneous disease with frequent comorbidities, which was highlighted by the 2018 EULAR evidence-based recommendations for gout diagnosis [1]. In this Update, comorbid conditions are considered when assessing risk factors for gout flare and other related conditions. Additionally, the guidelines offer more precise and robust recommendations, regarding urine alkalization for individuals with hyperuricemia and gout. The EP agreed that citrate preparations should be preferred for urine alkalization due to their efficacy, potential kidney protective effects, and anti-inflammatory properties [6, 25, 26]. Due to the same concern about the potential harm of gout flares, the Update also recommends a gout diagnostic framework for patients without verified hyperuricemia.

The role of lifestyle factors in the development of hyperuricemia and gout is well-established. In addition to dietary limitations, the 2024 Update provides prioritized dietary recommendations with certain nutrients that recently proved to be beneficial for urate reduction and gout management. Based on evidence [6, 32, 33], the EP endorses the consumption of dietary fiber,

tart cherry products, citric acid, and skim milk, which may help manage gout and improve patient outcomes.

Compared to the 2019 Guidelines and other previously published recommendations, this 2024 Update incorporates a deeper understanding of the disease and integrates the latest evidence, especially studies from the Chinese population, broadening its applicability in diverse clinical scenarios. However, certain recommendations remain based on limited research, which necessitates ongoing investigation, especially regarding long-term cardiovascular and renal outcomes. Clinical questions involving gout with comorbidities will be addressed in part two of this guideline.

Author Contributions

Changgui Li conceived the idea and submitted the project with a contribution from Zhaohui Lyu to the Chinese Association of Endocrinology Executive Committee. Jiajun Zhao organized and chaired the meetings. Changgui Li was in charge of the whole process of the guideline development. Mingshu Sun wrote the manuscript with the help of Can Wang and Zhen Liu. Wen-Chan Tsai and Ronald M.L. Yip provided opinions as external reviewers. All authors have contributed to this work and have approved the final version of the manuscript.

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Ethics Statement

This study does not involve human participants.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.